1. My name is Sander Greenland. I am a Professor of Epidemiology, UCLA School of Public Health and Professor of Statistics, UCLA College of Letter and Science.
2. I was retained by the Plaintiffs to review the epidemiologic data concerning Neurontin (gabapentin) and suicidality and to render opinions concerning the epidemiologic evidence concerning the relationship of Neurontin to suicidality.
3. As part of my tasks, I reviewed the company's submission of data to the FDA as well as the FDA's analysis of the data. I also reviewed the expert reports and materials of Defendant's expert Dr. Robert Gibbons. In performing my assignment, I used the same methodologies that I use in my routine scientific activities.
4. I hold the following opinions to a reasonable degree of scientific certainty
    a. It is my opinion that the data that Pfizer provided to the FDA as part of its response on suicidality and Neurontin did not show that Neurontin does not cause suicidal behavior and ideation (suicidality).
    b. In reaching its conclusion that Neurontin and other drugs increase the risk of suicidality, the FDA used sound methods and the analysis was conducted correctly. I concur with the FDA's analyses.
    c. New reports support the FDA's conclusions and mine regarding the association of Neurontin with suicidality.
    d. Pfizer's expert Dr. Robert Gibbons' opinions on the FDA alert are deceptive and are biased.
    e. Dr. Gibbons' expert reports are so flawed and biased that they have no scientific validity and should be dismissed. In particular, they present conclusions that cannot be supported by the data they discuss and which are in fact absent from the publications discussing the data, showing that those conclusions have been tailored for the defendant rather than reached by any sound scientific methodology from the data presented.
    f. Dr. Gibbons' papers suffer from the usual methodologic problems associated with data base studies of this type and cannot be taken as showing that Neurontin prevents or causes suicidality.

    I will now explain each of these opinions.

5. During the 2004-2007 time frame, Pfizer provided the FDA with several analyses of adverse events in both clinical trials and post-marketing use. I reviewed these documents from Parsons, Mohan, and Evertz. It is my opinion that these materials provide no evidence regarding the presence or absence of a relation of gabapentin to suicide. This is because the Parsons reports and the subsequent data in the Evertsz letter had no completed suicide and only one suicide attempt among controlled comparisons, while the data in the Mohan report could not and hence did not provide a valid suicide-rate calculation for gabapentin users, or a controlled comparison of users and nonusers.

    The absence of extensive epidemiologic evidence regarding the relation of gabapentin to suicide risk may be explained in large part by the nature of the outcomes being studied. Completed suicide is a rare event. For example, among

patient populations for which gabapentin was prescribed, the first Parsons report counted only 1 suicide during the 4,500 patient-years of follow-up. Assuming a rate of only 1 per 4,500 patient years among the exposed, I estimate that even a randomized placebo-controlled trial would need well over 400,000 patient-years of total follow-up to have an 80% chance of detecting a doubling of the rate due to gabapentin, using a 0.05 alpha-level statistical test. Under the same assumptions, if attempted suicides occur at 8 times the rate of completed suicides, the number of patient-years required to detect a doubling of the attempted-suicide rate would be well over 50,000, and the study would face the additional difficulty of having to detect suicide attempts. Studies of such enormous size would be infeasible under ordinary circumstances, and the size required explains why the current evidence from controlled clinical trials and epidemiologic studies is so limited.

6. In January, 2008, the FDA issued an alert that anti-epileptic drugs, including Neurontin, may increase the risk of suicidal behavior or ideation. The FDA found that these drugs were associated with an 80% increase in risk in randomized placebo-controlled trials. This means that trial subjects who were given one of these drugs were twice as likely to show suicidal behavior or ideation as those who were given a placebo (an inert pill) instead.

   In May, 2008, after the alert was issued, the FDA provided details of how they determined that there was an increased risk. I reviewed this document, Based upon my experience, the FDA properly reviewed the data and their conclusions are well founded. The FDA also looked at the data many different ways to make sure of their results. This was the right thing to do, and no matter which way they looked at the data, the results all pointed to the same conclusion- these drugs increase the risk of suicidal behavior.

   This is not just my opinion. A panel of more than 20 independent scientists and experts reviewed the FDA's work at a public hearing. On the panel were three scientists who are experts in statistics and who had no criticisms of the FDA's work. Pfizer had an opportunity to present their opinion that Neurontin does not cause suicidal behavior, but the FDA reviewed what Pfizer had to say and rejected their opinions.

7. There are now several studies that support the FDA’s conclusions. Most relevantly, in the April 14, 2010 issue of Journal of the American Medical Association (JAMA), p. 1401-1409, Patorno et al. report on some 300,000 treatment episodes, including over 140,000 with Neurontin (gabapentin). They reported observing increased risk of suicidal acts for gabapentin, lamotrigine, oxcarbazepine , tiagabine, and valproate compared with topiramate. The rate of suicidal acts among gabapentin users was1.42 times (42%) higher than that in topirimate users (95% confidence interval 1.11 to 1.80). In Figure 2 of the 2008 FDA report, topirimate patients showed 2.53 times the suicidality risk of placebo patients in clinical trials. Thus, relative to a placebo, the excess of risk seen for

gabapentin relative to topirimate would correspond to 1.42 times 2.53, or a 3.6-fold increase in risk.

Next, in the journal Pharmacoepidemiology and Drug Safety, Olesen et al. (2010) reported a study of 6,780 suicides in Denmark in which they estimated antiepileptic treatment initiation to increase the risk of suicide by 1.84-fold (84%) with a 95% confidence interval 1.36 to 2.49. Figure 1 of that paper reported significantly elevated risks for clonazepam, valproate, lamotrigine and phenobarbital, and statistically nonsignificant increased risks for gabapentin and topirimate. The reported increase for gabapentin was 2.2-fold (120%) with a 95% confidence interval from 0.83 to 5.83. The risk increases observed in this study statistically more consistent with the 2008 FDA observations of increased risk and the similar findings just mentioned by Patorno et al. than with the claims of no harm made by Dr. Gibbons.

Both of these studies are database studies, as is Dr. Gibbons' study, thus subjecting them to the same sort limitations that afflict Dr. Gibbons' study. Nonetheless, it is worth noting that neither study was funded by Pfizer or other party with an interest in this litigation, and the consistency of both studies with FDA conclusions and disagreement with Dr. Gibbons conclusions is in my opinion quite striking,

8. Dr. Robert Gibbons opinions on the FDA alert are so biased that they are unreliable. He makes statistical statements that are not based on sound methodology. He also makes serious statistical errors, every one of which is in favor of Pfizer; yet the average reader would have no way to recognize these errors.

   Contrary to Dr. Gibbons' claims, the FDA Statistical Review and the data reported therein provide no basis for claiming inconsistency between effects of gabapentin and the other drugs considered, including lamotrigine and topirimate. The statistical evidence in the gabapentin data alone are compatible with gabapentin having an effect similar to lamotrigine or topirimate, and are also compatible with gabapentin having no effect and gabapentin having a larger effect than the other drugs. Hence the FDA relied on physiologic arguments as well as meta-analysis to determine that the effects of gabapentin, lamotrigine, topirimate, and the other drugs examined are probably similar. The FDA examined 11 drugs and determined that 8, including gabapentin, exhibited positive relations to suicidality in placebo-controlled trials. They also found an overall relation of the drugs to suicidality that was significant by all usual standards. I thus concur with the July 10 vote of the FDA DSaRM Advisory Committee, agreeing with the FDA finding of increase in suicidality for the drugs examined.

9. Dr. Gibbons' opinion that his studies establish that gabapentin is protective of suicide or at least has no effect appears to be tailored exclusively for this litigation

rather than founded on any sound scientific inference method. No such claim can be found in the peer-reviewed material published by Dr. Gibbons and colleagues. In their published bipolar paper, Dr. Gibbons and colleagues acknowledge that his data only “suggests a possible protective effect of AED treatment on suicidality" (Gibbons et al., 2009, p. 1358). Since gabapentin is an AED, this statement shows that there is an inadequate basis for Dr. Gibbons to conclude that gabapentin is protective for suicidality.

The type of study performed by Dr. Gibbons is commonly done to investigate possible drug effects, and the statistical methods used by Dr. Gibbons are conventionally accepted as statistical summaries of the observations. Nonetheless, the causal inferences drawn by Dr. Gibbons are not warranted by the type of study, analyses, and summaries that he presents. There is a large analytical gap between his statistical results and his causal conclusions, and Dr. Gibbons continues to present no analysis that accounts for that gap, even though methods to do so are abundant in the statistical and epidemiologic literature. His failure to apply or even mention these methods may be because such methods demonstrate that causal conclusions from studies like his are unwarranted.

It is my opinion that this problem is especially severe in the present case, because data obtained by Dr. Gibbons failed to include all of the relevant drugs taken by the patients. That data was readily available to him for purchase and should have been obtained and used in the analysis. In addition, while he could have accurately determined whether an individual was on or off the drug prescription at the time of the attempt, he instead performed various sensitivity analyses that in never addressed the issue appropriately.

Therefore, while Dr. Gibbons used a common study design and accepted statistical methods for estimating associations, he failed to obtain adequate data to address concerns about confounding, and failed to properly apply his methods to the data. Furthermore, he never attempted to account for the uncertainties about the gaps between his data, his analyses, and his causal conclusions. As such, the conclusions he expresses in his expert reports are scientifically unwarranted and unreliable. Thus, I do not agree that he is applying sound scientific principles when he claims that his studies demonstrate gabapentin does not increase the risk of suicide.

In sum, Dr. Gibbons has conducted studies and analyses of a form routinely performed within the scientific community. Nonetheless, his conclusion that gabapentin does not increase the risk of suicidal behavior does not follow from his studies and analyses. Furthermore, all other studies published to date of which I am aware are independent of litigation and support instead the hypothesis that gabapentin increases risk of suicidality.

In light of the data and analysis problems I have described above, it is my opinion that no statistically or scientifically reliable inference or conclusion about the

effects of gabapentin can be drawn from the statistical analyses presented by Dr. Gibbons in his expert reports and by Gibbons et al. (2009). Furthermore, no statistical analysis of the data obtained by Dr. Gibbons could provide a scientifically reliable conclusion about gabapentin effects.